Tumor Immunology

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TEACHING OBJECTIVES:

1. Know the evidence for immune reactivity to tumor
2. Know the changes in cellular characteristics due to malignancy
3. Know the host components which affect tumor progression
4. Know the tumor cell components which protect it from the immune system
5. Understand the rationale for tumor immunotherapy and know the approaches

READING:

Roitt, Brostoff and Male: Immunology, 6th Ed., Chapt. 18.

Evidence for immune reactivity to tumor:

Tumors that have severe lympho-reticular infiltration have a better prognosis. Certain tumors regress spontaneously (*e.g.*, melanomas, neuroblastomas). There is an increased incidence of malignancies (particularly lympho-reticular tumors) in immunodeficient patients (primary and secondary). Antibodies and immune T lymphocytes (in cytotoxicity and mitogenic response assays) have been detected in patients with tumors. Finally, animals can be specifically immunized against various types of tumors.

Tumor associated antigens:

In order for the immune system to react against a tumor, they must have antigens that are recognized as foreign. A number of alterations occur in the cell during tumorigenesis (derepression of some genes, repression of others, or alteration of genes via mutation). Most relevant from the point of view of immuno-surveillance are surface membrane molecules that might be antigenically novel or suppression of membrane proteins that are essential for immune recognition and activation.

In animals, most tumors induced by physical, chemical, or viral agents express **neo-antigens**. By contrast, spontaneously occurring tumors are often only weakly immunogenic or non-immunogenic.

Antigenic changes observed in malignant cells include reappearance of embryonic proteins not expressed in the adult life (**oncofetal antigens**), and expression of unique antigens not expressed by normal cells. Some of these antigens may be secreted while others are membrane-associated molecules. Neo-antigens that contribute toward tumor rejection are referred to as **tumor associated transplantation antigens** (**TATA**).

Onco-fetal antigens:

Oncofetal antigens may appear due to de-repression of preexisting genes. Two major oncofetal antigens are **alpha-fetoprotein** (**AFP** and **carcino-embryonic antigen** (**CEA**). AFP is produced only as a secreted protein whereas CEA is found both on cell membrane and in fluids. Since secreted antigens contribute little toward immunity against tumors, the role of these neo-antigens in immuno-surveillance is questionable. However, they can aid in monitoring the progression of certain tumors and their response to treatment.

Alpha-fetoprotein:

The normal range of AFP concentration in humans is 0-20 ng/ml. This level rises considerably in patients with hepatoma and non seminal testicular carcinoma. A 5-fold or higher rise in this protein is used for monitoring hepatomas and testicular cancers. AFP level may also be raised in some nonmalignant conditions, such as cirrhosis, hepatitis and other forms of liver damage.

Carcinoembryonic antigen:

CEA levels in normal individuals are below 2.5 ng/ml, but it increases significantly in certain malignancies, particularly colo-rectal cancers. It may also rise in some nonmalignant conditions (*e.g.*, chronic cirrhosis, pulmonary emphysema, heavy smoking). Levels 4-5-fold of normal have been used to predict recurrence of colo-rectal tumors.

Tumor associated transplantation antigens (TATA) on viral tumors:

A number of viruses cause different types of tumors in animals (SV-40, adeno, Rouse, Friend, Moloney Rauscher and Gross viruses). Viruses are involved or suspected to be involved in some human malignancies (*e.g.*, HTLV-1 in leukemia, hepatitis-B virus in hepatic carcinoma, papilloma virus in cervical cancer). Virus-induced tumors express cell surface antigens (distinct from antigens of the virion) which are shared by all tumors induced by the same virus. These antigens are characteristic of the tumor-inducing virus regardless of tissue origin of the tumor or animal species in which the tumor exists (Figure 1).

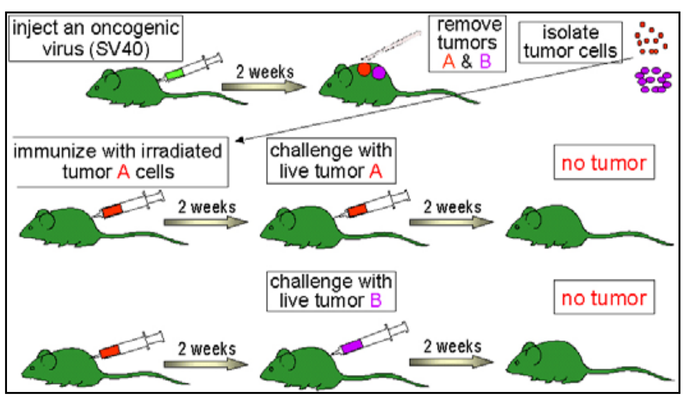


Figure 1. Common antigens on virus-induced tumors

Tumor associated transplantation antigens on chemically induced tumors:

chemically induced tumors are different from virally induced tumors in that they are extremely heterogeneous in their antigenic characteristics. Thus, any two tumors induced by the same chemical, even in the same animal, rarely share common tumor specific antigens (Figure 2). These unique antigens on chemically induced tumors are referred to as **tumor specific transplantation antigens (TSTA)**.

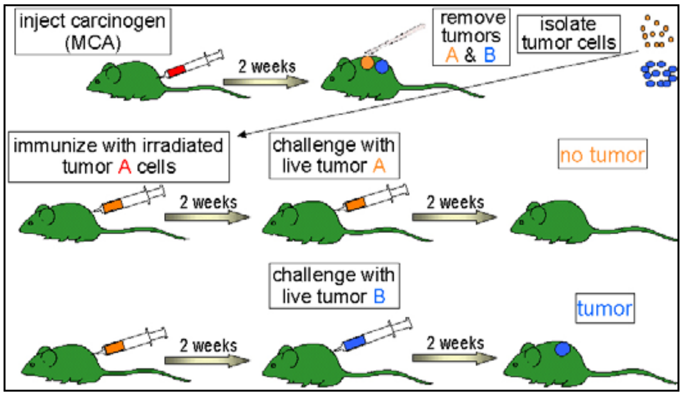


Figure 2. Demonstration of tumor-specific transplantation antigens on chemically induced tumors

Immunity against tumors:

A direct evidence for immunity against malignancy comes mostly from experimental tumors, although there is ample indirect evidence for anti-tumor immune reactivity in humans. In experimental studies, animals can be immunized by administering inactivated tumor cells or by removal of a primary tumor. Also, immunity can be transferred from an animal, in which a tumor has regressed, to a naive animal by injection of lymphocytes (T cells). All components of the immune system (nonspecific and specific; humoral and cellular) can affect the growth and progression of a tumor.

Escape from immuno-surveillance:

A number of mechanisms have been suggested for the escape of malignant cells from host immuno-surveillance. Tumors may not express neo-antigens that are immunogenic or they may fail to express co-stimulatory molecules for the activation of T-cells. In addition certain tumors have been known to lack or be poor in expression of MHC antigens.

Another reason for failure of immunosurveillance may be the fact that in the early development of a tumor, the amount of antigen may be too small to stimulate the immune system and due to the rapid proliferation of malignant cells, the immune system is quickly overwhelmed. In addition, some tumors may evade the immune system by secreting immunosuppressive molecules and others by inducing suppressor cells. Also, some tumors may shed their unique antigens which block antibodies and T cells from reacting with malignant cells.

Use of tumor neo-antigens in patient management

The presence of neo-antigens on tumor cells has been exploited for both diagnostic and therapeutic purposes.

Immuno-diagnosis:

Monoclonal antibodies labeled with radioisotope have been used for *in vivo* detection of relatively small tumor foci. Antibodies have also been used *in vitro* to identify the cell origin of undifferentiated tumors, particularly of lymphocytic origin (*e.g.*, CALLA: CD10). Also, immunohistological staining is used to confirm suspected metastatic foci, especially in bone marrow.

Immunotherapy:

Immunotherapy has been used as adjunct to the traditional treatment. Both active and passive means of stimulating the nonspecific and specific immune systems have been employed, in some cases with significant success (Table 1).

Table 1. Immunotherapy of tumors

active	non-specific	BCG, *Propionibacterium acnes*, cytokine genes, *etc*.
	specific	killed tumor cells or their extract, recombinant antigens, idiotype, co-stimulatory molecule genes, *etc*.
passive	nonspecific	LAK cells, cytokines
	specific	antibodies alone or coupled to drugs, pro-drug toxins or radioisotope; bispecific antibodies; T-cells
	combined	LAK cells and bispecific antibody

. * BCG: Bacillus Calmette Geurin is a bovine strain of *Mycobacterium tuberculosis*.

A variety of immunopotentiating agents (biological response modifiers) are used to enhance anti-tumor immunity. They include bacterial products, synthetic chemicals and cytokines (Table 2). Most of these agents exert their effects by activating macrophages and NK cells, eliciting cytokines or enhancing T-cell functions.

Table 2. Non-specific active immunotherapy: biological response modifiers (BRMs)

type of BRM	examples	major effect
bacterial product	BCG, *P. acnes*, muramyl di-peptide, trehalose dimycolate	activate macrophages and NK cells (via cytokines)
synthetic molecules	pyran, poly I:C, pyrimidines	induce interferon production
cytokines	interferon-α, -β, -γ, IL-2, TNF	activate macrophages and NK cells

A number of cytokines have been used to potentiate the immune function of the host since the discovery that these cytokines have potent and selective effects on certain components of the immune system (Table 3).

Table 3. Cytokine therapy of tumors

cytokine	tumor type and result	antitumor mechanism(s)
IFN-α, β	remission of hairy cell leukemia, weak effect on some carcinomas	increased expression of class I MHC, possible cytostatic anti-tumor effect,
IFN-γ	remission of peritoneal carcinoma of ovary: ineffective systemically	increased MHC antigens; macrophage, Tc and NK cell activation
IL-2	remission in renal carcinoma and melanoma	T-cell proliferation and activation, NK cells activation
TNF-α	can reduce malignant ascites	macrophage and lymphocyte activation

Monoclonal anti-tumor antibodies have been used for indifferent forms for the treatment of cancer, because of their direct effect or as vehicles to target anti-cancer drugs, toxins and the nonspecific components of the host's immune system to the site of tumor (Figure 3). In addition, such specific antibodies are also used in the diagnosis of metastatic lesions, otherwise not detectable by conventional radiologic means.

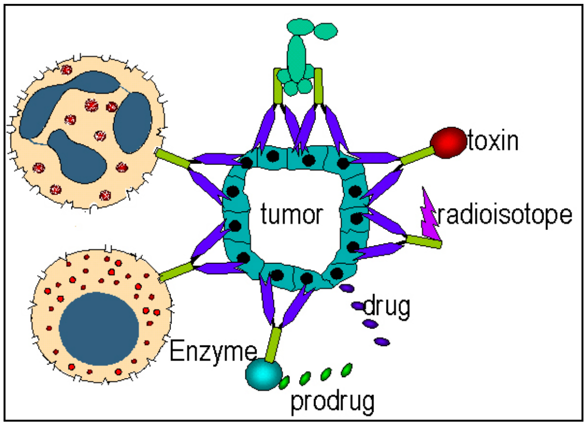


Figure 3. Therapeutic and diagnostic uses of anti-tumor antibodies